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November 27, 2002

Date: 11/27/02

Signature: Margaret H. Sundge

Attorney Docket No. 9950-0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:  
ULRICH et al.

U.S. Serial No.: 09/402,273

Group Art Unit: 1644

U.S. Filing Date: December 13, 1999

Examiner: P. Huynh

International Application No.: PCT/EP98/02138

International Filing Date: 03 April 1998

Title: ALLERGEN FORMULATION

**DECLARATION OF DEREK RICHARDSON**  
**SUBMITTED PURSUANT TO 37 C.F.R. § 1.132**

Commissioner for Patents  
Washington, DC 20231

Sir:

I, Derek Richardson, hereby declare that:

1. I have been requested by Louis L. Wu, an attorney of record on the patent application identified above, to review the application and the pending claims, the August 27, 2002 Office Action, the response to the Office Action which accompanies this declaration, International PCT Publication Nos. WO 96/34626 and WO 92/16556, and U.S. Patent No. 5,795,862 to Frank et al. I am not an inventor of the subject matter sought to be patented in the subject patent application.

2. It is my understanding that the pending claims were rejected as obvious over the combination of the three cited references. I have been informed that "obviousness" in this context means that the differences between the subject matter sought to be patented and the cited references are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. I have also been informed that unexpected results and commercial success are indicia of nonobviousness.

3. In connection with the present analysis, I have reviewed the subject patent application and the pending claims, the August 27, 2002 Office Action, the accompanying response and the cited references. My opinions as set forth herein are based on my understanding of the claimed invention and the cited references, and are drawn from my knowledge of the inventive subject matter and of the art of allergen compositions.

#### QUALIFICATIONS

4. I am employed by Allergy Therapeutics Limited, the assignee of the subject patent application. My title is Technical Development Manager a position I have held since June 1998. Prior to my employment at Allergy Therapeutics, I held the positions of Allergy Department Manager and Technical Development Manager with SmithKline Beecham Pharmaceuticals. I am a Chartered Biologist and Member of the Institute of Biology and hold a Post Graduate Diploma in Microbiology from Chelsea College of Science and Technology London University 1963 -1965.

#### QUESTION

5. The question to which I have directed my attention is as above, i.e., whether, in my opinion, the claimed invention is obvious over the combined teaching of International PCT Publication Nos. WO 96/34626 and WO 92/16556, and U.S. Patent No. 5,795,862 to Frank et al.

#### OPINION

6. I understand that each of the claims at issue involves "a pharmaceutical composition capable of selectively enhancing a TH<sub>1</sub> response over a TH<sub>2</sub> response." I also understand that the composition is comprised of tyrosine, an allergen or allergen extract, and 3-DMPL.

7. Upon my review of the materials which I address below, it is my opinion that the claimed pharmaceutical composition is nonobvious in view of the cited references.

8. My determination of nonobviousness is based, in part, on my review of the cited references, individually and in combination with each other, in view of my knowledge of the art of allergen compositions.

9. I am aware that, at the time of the subject application's filing, a variety of adjuvants such as aluminum salts and naturally occurring amino acids (e.g., L-tyrosine) have been employed to enhance general immune responses to antigens with which they are administered. In particular, I am aware that aluminum salts are the most widely used adjuvants for inducing protective immunity against bacterial, viral infection and toxemia and that aluminum salt-based adjuvants are the only ones registered for clinical use in many countries.

10. It is my understanding that the immune response involves a complex series of controlled events with various feed back mechanisms, checks and balances. In addition, there are many different types of antigen-specific antibodies. For example, viral infection and toxemia can be countered by the induction of high levels of specific IgG antibodies. Infection at mucosal surfaces induces antigen-specific IgA antibody. Parasite infection is characterized by a high level of induced parasite-specific IgE antibodies.

11. Recently, the immune response has been mechanistically classified into two categories, TH<sub>1</sub> and TH<sub>2</sub>. In addition, certain antigen-specific antibodies are associated with each category. For example, aluminum salt adjuvants tend to enhance a TH<sub>2</sub> response. Similarly, DMPL tends to enhance TH<sub>1</sub> activity in experimental animals. A variety of adjuvants are discussed in the cited references without specificity as to the category of immune response that would be induced by the co-administration of the antigen and an adjuvant.

12. It is my opinion that while each of the cited references teaches that co-administration of an antigen with an adjuvant induces an immune response, the references together contain insufficient disclosure regarding specific antibodies and the category of immune response. There is nothing in the cited references to suggest that a composition comprising tyrosine, an allergen or allergen extract, and 3-DMPL would selectively enhance a TH<sub>1</sub> response over a TH<sub>2</sub> response.

13. My determination of nonobviousness is also based in part on the disclosure contained in the subject patent application.

14. From my review of the data presented on page 6 of the subject application, it is unexpected that the composition containing tyrosine, an allergen or allergen extract (e.g., ovalbumin) and 3-DMPL would enhance an IgG2 antibody response to a level that is approximately three orders of magnitude higher than the IgG2 response to a composition containing the same allergen or allergen extract with either one of tyrosine and 3-DMPL.

15. It is also unexpected that composition containing tyrosine, an allergen or allergen extract (e.g., ovalbumin) and 3-DMPL would not significantly enhance IgE antibody response when compositions containing the same allergen or allergen extract with either one of tyrosine and 3-DMPL alone more than doubles the IgE antibody response.

16. It is further unexpected that composition containing tyrosine, an allergen or allergen extract (e.g., ovalbumin) and 3-DMPL would enhance an IgG2 response over an IgE antibody response.

17. It is therefore my opinion that the claimed composition would likely to be significantly more effective, safer and more convenient than existing pharmaceutical compositions for selective enhancement of the  $TH_1$  response over the  $TH_2$  response.

18. My determination of nonobviousness is further based in part on my knowledge that Allergy Therapeutics has successfully introduced a commercial product based on the claims of the subject application.

19. Attached to my declaration as Appendix A is a brochure from Allergy Therapeutics that describes a vaccine product that has been commercially marketed under the trademark POLLINEX Quattro<sup>®</sup>. As demonstrated by the brochure, the product contains tyrosine and 3-DMPL in combination with one to four allergoids selected according to an individual's particular needs. Exemplary allergoids listed include grasses plus rye, birch, three trees (birch/alder/hazel), mugwort, plantain, olive, parietaria and ragweed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date:

27<sup>th</sup> November 2002



Derek Richardson

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Atty Dkt No. 9950-0002  
Serial No. 09/402,273

APPENDIX A  
BROCHURE FOR POLLINEX QUATTRO®